Deaths in Dexmedetomidine Clinical Studies
As Reported by: October 5, 1999

	Number of Deaths				
	By Treatment				Total
	Dex	Placebo	Active Control	None*	
Phase I					
Abbott	0	0	0	0	0
Orion	0	0	0	0	0
Total	0	0	0	0	0
Phase II - Abbott					
W97-249	1	0	0	0	1
W98-263	4	0	0	0	4
W98-264	2	0	0	0	2
W98-274	0	1	0	0	1
Total	7	1	0	0	8
Phase II - Orion					
F-DEX-CL-0192-USA	0	1	0	0	1
3005006	1	1	0	0	2
Total	1	2	0	0	3
Phase II - Abbott + Orion	8	3	0	0	11
Phase III - Abbott					
DEX95-002	2	1	0	0	3
DEX95-004	2	1	0	0	3
DEX96-014	0	1	0	0	1
DEX96-015	3	2	0	0	5
DEX96-021	1	0	0	0	1
W97-245	0	8	0	3	11
W97-246	7	3	0	1	11
Total	15	16	0	4	35
Phase III - Orion					
3005003	0	1	0	0	1
Phase III - Abbott + Orion	15	17	0	4	36
Phases I, II, III					
Abbott	22	17	0	4	43
Orion	1	3	0	0	4
Total	23	20	0	4	47
Academic -GBNI99-102	2	0	0	0	2
* Treatment is 'None' if death occurred prior to treatment					
SOURCES:					
Abbott Studies - SAGE Report 05Oct99					
Orion Studies - Synopses					
GBNI99-102 - SAGE Report 05Oct99					

ABBOTT
Hospital Products Division
200 Abbott Park Rd.
Abbott Park, IL 60064-3537

To: Dr Susmita Samanta

Company:

FAX #: 301-480-8682

Date: 10/5/99

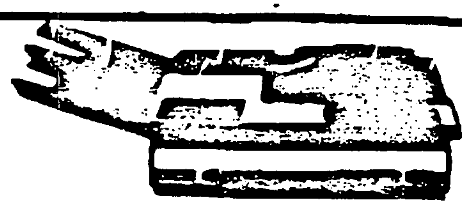
No. of Pages: 4 (including cover page)

From: Jean Conaway
Regulatory Affairs D389/AP30

(847) 937-3413 (telephone)
(847) 938-7867 (fax)

Here is a working draft copy of the cover letter only.
The original will be federal expressed 10/6/99 to the
address on the letter

Jean Conaway



ABBOTT

Hospital Products Division
Abbott Laboratories
D-389, Bldg. AP30
200 Abbott Park Road
Abbott Park, Illinois 60064-3537

October 5, 1999

CENTER FOR DRUG EVALUATION AND RESEARCH
ANESTHETIC, CRITICAL CARE & ADDICTION DRUG PRODUCTS, HFD #170
Attn: DOCUMENT CONTROL ROOM #9B-23
5600 Fishers Lane
Rockville, Maryland 20857-1706

ATTENTION: Cynthia McCormick, M.D.
Director

Fax: Dr. Susmita Samanta
301-480-8682

Re: NDA 21-038 Dexmedetomidine Hydrochloride Injection

Abbott Laboratories hereby amends the above-referenced new drug application for the subject drug product to provide for Case Report Forms (CRFs) and a table for the nine specified patients. We are responding to the teleconference on October 4, 1999 between Dr. Patricia Hartwell and Dr. Susmita Samanta, FDA and Dr. Thomas Willer, Abbott Laboratories.

The Agency requested the following:

REQUEST: **Please provide CRFs for all nine deaths specified in the teleconference between the Agency and Abbott Laboratories on September 28, 1999 and reported in the amendment dated October 1, 1999.**

RESPONSE: The nine patients reported in the amendment dated October 1, 1999 are as follows:

Study No.	Patient Number	CRF Available	PCA No./ Related or Unrelated	Study Drug
W97-245	#01001*	Yes	9906355- Unrelated	Placebo-died 5 days post-study
W97-245	#10401*	Yes	9907455- Unrelated	Placebo-died 12 days post-study
W97-245	#105	No	9905913- Unrelated	None received
W97-245	#6301	No	9906686- Unrelated	None received
W97-245	No # assigned**	No	9906525- Unrelated	None received
W97-246	#704	No	9907483- Unrelated	None received
W97-246	#12406*	Yes	9907027- Unrelated	Placebo- died 35 days post-study
W97-246	#11601	Yes	9906654- Unrelated	Dexmedetomidine- died 5 days post-study
3005003 (Orion)	#0901	Yes	9904548-Probably not related	Placebo- died 1 month post-study

*Included in the Integrated Summary of Safety, Appendix B, submitted as part of NDA-21-038, Volume 301 of 726, page 8/10-238-162. Not included in the clinical safety database.

**Consent form signed, but patient was not randomized prior to the start of surgery. Patient died intraoperatively.

Provided in EXHIBIT I are Case Report Forms for the following five patients:

01001, 010401, 012406, 011601, 0901.

The Case Report Forms for the remaining four patients will be sent to the Agency as soon as available.

REQUEST: **Please provide a table which includes the number of deaths according to the following:**

1. **Groups: dexmedetomidine, placebo and active control groups,**
2. **Sponsor: Abbott , Orion and total,**
3. **Clinical Study Phase: Phase I, II and III.**

RESPONSE: The above request is acknowledged and will be provided as soon as available.

Cynthia McCormick, M.D.
Page Three
October 5, 1999

If you have any additional questions, please do not hesitate to contact me at (847) 937-3413 or after October 7, 1999, Dr. Thomas Willer at (847) 937-6845.

Sincerely,

ABBOTT LABORATORIES

Jean M. Conaway

Jean M. Conaway, R.Ph.
Manager, Regulatory Affairs
Hospital Products Division
Phone: (847) 937-3413
Fax: (847) 938-7867

JMC:jmc

G:\10-99\fda.jmc.doc1

APPEARS THIS WAY
ON ORIGINAL

ABBOTT

Hospital Products Division
Abbott Laboratories
D-389, Bldg. AP30
200 Abbott Park Road
Abbott Park, Illinois 60064-8157

October 1, 1999

CENTER FOR DRUG EVALUATION AND RESEARCH
ANESTHETIC, CRITICAL CARE & ADDICTION DRUG PRODUCTS, HFD #170
Attn: DOCUMENT CONTROL ROOM #9B-23
5600 Fishers Lane
Rockville, Maryland 20857-1706

ATTENTION: Cynthia McCormick, M.D.
Director

Re: NDA 21-038 Dexmedetomidine Hydrochloride Injection

Abbott Laboratories hereby amends the above-referenced new drug application for the subject drug product. The FDA and Abbott Laboratories conducted a teleconference on September 28, 1999. Participating for the FDA were the following individuals: Dr. R. Rapapport, Assistant Division Director; Dr. P. Hartwell, Medical Reviewer; and Dr. S. Samanta, Project Manager. Participating for Abbott Laboratories were Ms. J. Sayre, Senior Operations Manager; Ms. R. Tiehen, Senior Regulatory Affairs Associate; and Dr. T. Willer, Associate Director, Regulatory Affairs. The Agency requested explanations for why the deaths of nine patients were duly noted in the 1999 Annual Progress Report but did not appear in NDA 21-038.

Please refer to Section 11 of the Integrated Summary of Safety (Additional Serious Adverse Event Reports from Abbott-Sponsored Studies) in the NDA. It reads as follows:

> "Abbott Laboratories' maintains a centralized database of serious adverse global events (SAGE). This database includes all serious adverse events reported for subjects/patients from the time informed consent is signed to at least 30 days after participation in an Abbott-sponsored study.
>
> Serious adverse events reported for subjects/patients within 24 hours (48 hours for Study DEX-95-004) of participation in an Abbott-sponsored dexmedetomidine study were to have been included in the clinical database for the specific study and consequently in the overall safety database, in addition to their inclusion in the SAGE database. Serious adverse events reported for subjects/patients 24 hours (48 hours for Study DEX-95-004) after participation up to 30 days in an Abbott-sponsored dexmedetomidine study were to have been included in the SAGE database, but may not have been included in the clinical database for the specific study or in the overall safety database."

In order to accurately reflect the number of serious adverse events reported during the Abbott-sponsored dexmedetomidine clinical program, a reconciliation of the overall safety database and the SAGE database was performed (presented in Section 11 of the ISS, Tables 35 and 36).

The nine patients specified in the teleconference of September 28, 1999 are presented in tabular form, as follows:

Study No.	Patient Number	CRF Available	PCA No./ Related or Unrelated	Study Drug
W97-245	#1001*	Yes	9906355- Unrelated	Placebo-died 5 days post-study
W97-245	#10401*	Yes	9907455- Unrelated	Placebo-died 12 days post-study
W97-245	#105	No	9905913- Unrelated	None received
W97-245	#6301	No	9906686- Unrelated	None received
W97-245	No # assigned**	No	9906525- Unrelated	None received
W97-246	#704	No	9907483- Unrelated	None received
W97-246	#12406*	Yes	9907027- Unrelated	Placebo- died 35 days post-study
W97-246	#11601	Yes	9906654- Unrelated	Dexmedetomidine- died 5 days post-study
3005003 (Orion)	#901	Yes	9904548-Probably not related	Placebo- died 1 month post-study

*Included in the Integrated Summary of Safety, Appendix B, submitted as part of NDA-21-038, Volume 301 of 726, page 8/10-239-162. Not included in the NDA safety database.

**Consent form signed, but patient was not randomized prior to the start of surgery. Patient died intraoperatively.

Please note that four patients (105, 6301, patient from W97-245 for whom no number was assigned, and 704) died intraoperatively and never received study drug (either placebo or dexmedetomidine). These patients were never considered part of the study because they never entered the ICU and received study drug. Therefore, these patients were not included in the NDA safety database or in the clinical study reports.

Three patients (1001, 10401, and 12406) received placebo, but all died at least five days after the end of study drug infusion (5, 12 and 35 days, respectively). The study follow-up period defined by the protocols was 24 hours. Because these three deaths occurred more than 24 hours after completion of the study, they were not included in the NDA safety database. As noted above, they were included in the SAGE database and in narratives, which appeared in Appendix B of the ISS (Volume 301 of 726, page 8/10-239-162).

One Abbott patient (11601) who received dexmedetomidine died 5 days after study completion. Since the death occurred more than 24 hours after study completion, this patient was not included in the clinical study database. It would appear, however, that this patient was inadvertently omitted from Appendix B of the ISS.

One Orion patient (901) who received placebo died one month after study completion. This patient was submitted as part of NDA-21-038, Volume 541 of 726, page 8/10-237-263.

All patients were noted as "unrelated" or "probably not related" with regard to study drug causality.

If you have any additional questions, please do not hesitate to contact me.

Sincerely,

ABBOTT LABORATORIES

Thomas F. Willer

Thomas F. Willer, Ph.D.
Associate Director, Regulatory Affairs
Hospital Products Division
Phone: (847) 937-6845
Fax: (847) 938-7867
Internet: WILLETF@hpd.abbott.com

APPEARS THIS WAY
ON ORIGINAL

TFW:tw

g:10-99f.tfw/18

EXHIBIT I

(1) ONGOING CLINICAL STUDIES

- DEXMEDETOMIDINE HYDROCHLORIDE

(2) COMPLETED CLINICAL STUDIES SINCE SUBMISSION OF NDA (12/98)

- DEXMEDETOMIDINE HYDROCHLORIDE

ONGOING CLINICAL STUDIES-DEXMEDETOMIDINE HYDROCHLORIDE

Protocol Number: W98-263
Study Title: A Pilot Phase II, Multi-Center, Randomized, Placebo-Controlled, Double-Blind Study Evaluating the Safety and Efficacy of Dexmedetomidine in Medical ICU Patients (France, Canada, and U.K.)
Estimated Study Completion Q4, 2000
Estimated Final Report: Q1, 2001
Summary:
Part I: 16 of 21 patients complete. Part II: 0 of 24 patients complete.

The objective of the study is to evaluate the safety and efficacy of dexmedetomidine in medical patients being intubated and ventilated for a minimum of six hours and not more than 24 hours. Patients admitted to the ICU for pulmonary disease requiring intensive treatment (i.e., pneumonia, asthma, chronic obstructive airway disease (COPD), smoke inhalation, or postoperative patients [>72 hours postoperatively] who develop pulmonary or chest infections), patients with pancreatitis, myasthenia gravis, or neuropathy, such as Guillain-Barre syndrome are eligible for the study.

Patients enrolled in Part I of the study will receive open label dexmedetomidine, and patients enrolled in Part II of the study will be randomized to either dexmedetomidine or placebo. All patients may receive propofol and morphine if required as additional medication for sedation or analgesia respectively.

All patients will receive a loading dose of 1.0 mcg/kg over 10 minutes followed by a maintenance infusion at an initial rate of 0.4 mcg/kg/hr. Following the initial rate, patients will be maintained within the range of 0.2 – 0.7 mcg/kg/hr (France and Canada), titrated to maintain a Ramsay sedation score of $\geq$3 while intubated, and $\geq$2 after extubation. Four patients in the UK were completed under this dosing regimen, and it was decided to expand the range of maintenance infusion. Patients in the UK will be maintained within the range of 0.2 – 2.5 mcg/kg/hr, and may receive additional boluses of 12 mcg (3 ml) of dexmedetomidine if needed.

Patients requiring sedation beyond 24 hours will be enrolled into study W98-264.

Protocol Number: W98-264
Study Title: A Phase II, Multi-Center, Open-Label Study Evaluating the Safety and Efficacy of Dexmedetomidine in Medical ICU Patients (France, Canada, and U.K.)
Estimated Study Completion Q4, 2000
Estimated Final Report: Q1, 2001
Summary:
6 patients of 32 complete

Patients completing the 24 hour infusion in study W98-263 are eligible for study W98-264, in which all patients receive open-label dexmedetomidine for up to an additional 6 days.

Protocol Number: W98-266
Study Title: Phase I Single-Center, Open-label Study Evaluating the Pharmacokinetics and Pharamcodynamics of Dexmedetomidine in Pediatric Patients (Canada)
Estimated Study Completion Q3, 2000
Estimated Final Report: Q4, 2000
Summary:
1 of 18 patients complete

The objective of this study is to evaluate the pharmacokinetics and safety of a single intravenous dose of dexmedetomidine in pediatric patients between two and twelve years of age. Pediatric patients undergoing urological, abdominal, or other surgeries requiring general and epidural anesthesia and overnight stay in the hospital are eligible for the study.

A 10 minute infusion of dexmedetomidine will be administered 2 hours before induction of anesthesia. Dosing will be administered in an ascending dose-ranging fashion in three dose groups: 2.0 mcg/kg/hr for Group I, 4.0 mcg/kg/hr for Group II, and 6.0 mcg/kg/hr for Group III. In each group, four patients will receive dexmedetomidine, and two will serve as controls.

Protocol Number: W99-302
Study Title: A Phase IIIb, Multi-Center, Open-Label, Randomized Study Comparing the Safety and Efficacy of Dexmedetomidine to Propofol-Based Standard of Care, for ICU Sedation Following Coronary Artery Bypass Graft Surgery.
Estimated Study Completion: Q2, 2000
Estimated Final Report: Q4, 2000
Summary:
49 of 300 patients complete

Patients undergoing CABG surgery are eligible for this study in which patients are randomized to either dexmedetomidine or standard of care treatment with propofol. Dexmedetomidine infusion is initiated at time of last sternal wire, with a loading dose of 3.0 mcg/kg/hr for 20 minutes followed by an initial maintenance infusion of 0.4 mcg/kg/hr which is titratable between 0.2 and 0.7 mcg/kg/hr. Infusion will continue for at least 6 hours following extubation, for up to 24 hours total.

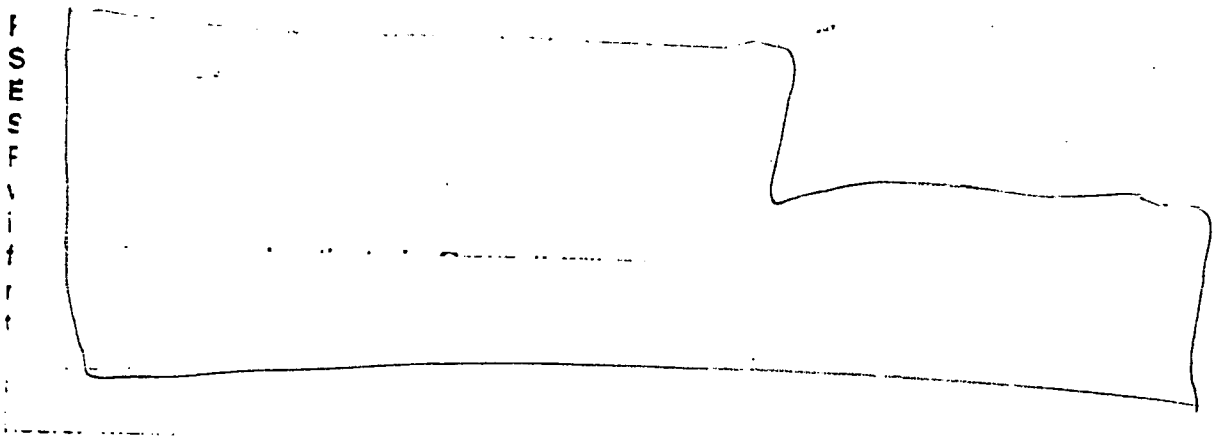
Protocol Number W99-294
Study Title European Study in Post-Op Patients in the ICU; Open study w/Dex
Estimated Study Completion Q2, 2000
Estimated Final Report: Q4, 2000
Summary:
00 of 500 patients complete

Patients undergoing major surgery requiring general anesthesia are eligible for this study, in which two loading doses of dexmedetomidine are compared. Dexmedetomidine infusion will be initiated at time of first suture. Patients in Group I will receive a loading dose of 6.0 mcg/kg/hr for 10 minutes, and patients in Group II will receive a loading dose of 3.0 mcg/kg/hr for 20 minutes. Both groups will receive an initial maintenance infusion of 0.4 mcg/kg/hr which is titratable between 0.2 and 0.7 mcg/kg/hr.

Infusion will continue through extubation and after extubation, for a recommended minimum of 6 hours. Maximum total infusion duration is 24 hours.

Protocol Number W99-314
Study Title CABG study in Latin America and S. Africa
Estimated Study Completion Not started
Summary

Patients undergoing CABG surgery are eligible for this study in which patients are randomized to either dexmedetomidine, or standard of care treatment with propofol. Dexmedetomidine infusion is initiated at time of last sternal wire, with a loading dose of 3.0 mcg/kg/hr for 20 minutes followed by an initial maintenance infusion of 0.4 mcg/kg/hr which is titratable between 0.2 and 0.7 mcg/kg/hr. Infusion will continue for at least 6 hours following extubation, for up to 24 hours total.



APPEARS THIS WAY
ON ORIGINAL

COMPLETED CLINICAL STUDIES SINCE SUBMISSION OF NDA (12/98) - DEXMEDETOMIDINE HYDROCHLORIDE

Protocol Number W98-272
Study Title: A Phase I, Single-Center, Double-blind, Randomized, Placebo-Controlled, Crossover Study Evaluating Dexmedetomidine as a Sedating Agent in Healthy Volunteers
Summary:
Eight healthy adult volunteers were to be enrolled. Each subject was to receive IV infusion of 0.2 mcg/hg/h dexmedetomidine HCl (low dose), 0.6 mcg/kg/h dexmedetomidine HCl (high dose), and a corresponding placebo via a standard syringe pump. Following an eight hour fast, subjects were to receive a 10-minute loading dose of 6.0 mcg/kg/h, followed by a 50-minute maintenance infusion of the designated study drug. Subjects randomized to placebo were to receive a loading dose of 0.9% sodium chloride solution.

The primary objectives of this study were to determine the sedative properties of low doses of dexmedetomidine in young, healthy volunteers, and to evaluate the effects of these low doses on analgesia, sedation, and cognitive function.

Final Report Submitted to FDA on May 12, 1999.

Protocol Number W98-273
Study Title: A Phase I, Placebo-controlled, Double-blinded, Dose Ranging Study to Evaluate the Effects of Dexmedetomidine on Sedation in Japanese Subjects.
Summary:
This trial designed as a two-part, Phase I, placebo-controlled, double-blinded trial in healthy subjects of ethnic Japanese origin. Part I was to consist of a dose-ranging study in approximately 40 subjects, 8 subjects per dose, to receive a 1-hour infusion. Part II was to consist of four long term infusion, dosing sessions in approximately 32 subjects, 8 subjects randomly assigned to each treatment group. Infusion times of 12 & 24-hours were to be studied.

The primary objectives were 1) to identify the dose/response relationship for sedation for single intravenous doses of dexmedetomidine, 2) to select and include 3 doses for the long term infusion portion of Part II of this study, and 3) to investigate the effects of long term infusions (12 & 24 hours) of dexmedetomidine on the sedative profile compared to single doses.

Final Report Submitted to FDA on September 3, 1999.

Protocol Number W98-274
Study Title: A Phase II Study entitled, "Alpha$_2$-Agonists as Components for Analgosedation in Intensive Care: Bispectral Index (BIS) Guided Sedation with Dexmedetomidine. A Randomized, Placebo-Controlled, Double-Blinded, Prospectrive Study".
Summary:
The objective the study was to evaluate the safety and efficacy of dexmedetomidine in patients requiring ventilation, sedation and intensive care for a minimum of 6 hours following surgery.

The primary efficacy variable for this study is the total dose of propofol required, in addition to study drug, to achieve adequate sedation, as deemed clinically necessary and as assessed by BIS, to achieve and maintain a BIS Score of 60 to 70 (indicating deep sleep) and a BIS Score of 85 to 95 after extubation (equivalent to a Ramsay Score of 2-3).

Study drug will be administered for a minimum of 6 hours prior to extubation and a minimum of 6 hours post-extubation. The Investigator may continue the infusion at his/her discretion for a maximum of 72 hours total study drug infusion.
Estimated Final Report: December, 1999

Protocol Number DEX-96-017

Study Title: Beta Blocker Interaction: A Phase II, Single-Center, Double-Blind, Randomized, Placebo-Controlled Study Evaluating the Effect of Esmolol on the Pharmacodynamics of Dexmedetomidine in Patients Undergoing Elective Cardiac Surgery.

Summary:

The primary objective of this study was to evaluate the impact of dexmedetomidine on hemodynamics following administration of a beta-blocker (esmolol) to patients undergoing elective cardiac surgery.

At least 40 adult, ASA Class II – IV patients (four in the esmolol dose-verification portion of the study and 12 per treatment group in the double-blind, placebo-controlled portion) scheduled for cardiac surgery were to be enrolled.

0.3 or 0.6 ng/ml of dexmedetomidine was to be administered from approximately 1 hour prior to the induction of anesthesia until 6 hours after the end of surgery.

Estimated Final Report: October, 1999

APPEARS THIS WAY
ON ORIGINAL

ABBOTT
Hospital Products Division

To: DR S SAMANTA

Company: FDA

FAX #: 301-480-8682
443-7068

Date: 9/21/99

No. of Pages: _____ (including cover page)

From: Dr. Tom Willer
Regulatory Affairs

(847) 937-6845 (telephone)
(847) 938-7867 (fax)

ABBOTT

Hospital Products Division
Abbott Laboratories
D-389, Bldg. AP30
200 Abbott Park Road
Abbott Park, Illinois 60064-6157

September 16, 1999

CENTER FOR DRUG EVALUATION AND RESEARCH
ANESTHETIC, CRITICAL CARE & ADDICTION DRUG PRODUCTS, HFD #170
Attn: DOCUMENT CONTROL ROOM #9B-23
5600 Fishers Lane
Rockville, Maryland 20857-1706

ATTENTION: Cynthia McCormick, M.D.
Director

Re: NDA 21-038 Dexmedetomidine Hydrochloride Injection

Abbott Laboratories hereby amends the above-referenced new drug application for the subject drug. We are responding to two telephone requests from the FDA to Abbott Laboratories.

(1) FDA-Abbott Laboratories Teleconference, September 14, 1999

[redacted]

FDA request (b) was for information pertaining to the collection of PK data in ongoing and future clinical studies. Pharmacokinetic data will be obtained from the following ongoing studies: W98-266 (Pediatric), W98-263 (Medical ICU Patients) and W98-264 (Medical ICU Patients). Final reports may be available in mid-2000. Abbott Laboratories is not in a position to project, at this time, what future studies will be conducted and which ones will or will not incorporate the collection of pharmacokinetic data.

(2) FDA-Abbott Laboratories Teleconference, September 16, 1999

A teleconference was held on September 16, 1999 among the following individuals: Dr. P. Hartwell, FDA Medical Reviewer; Dr. S. Samanta, FDA Project Manager; and from Abbott Laboratories: Dr. T. Willer Associate Director, Hospital Products Regulatory; Ms. P. Scaman, Associate Director, International Regulatory; Ms. R. Tiehen, Senior Regulatory Affairs Associate, International Regulatory; and Ms. J. Sayre, Senior Operations Manager, Dexmedetomidine Venture. The FDA requested that the paragraph pertaining to "Perioperative Studies" on page 5 of the annotated package insert be revised to remove all references to study Dex-96-012. The references deleted or modified include the following items:

Evaluated in "7" studies; Total of "1199" patients; With "761" receiving [redacted]
Target concentrations of "0.15"; Infusions of 15 minutes(002, 004, ~~012~~,.....); "1-hour (012)"

Dr. Hartwell further requested that a caveat be added to the last sentence of the paragraph mentioning that although the drug is "well tolerated," an increase in hypotension may be seen with dexmedetomidine, as stated in other sections of the package insert. Per FDA request, the paragraph entitled "Perioperative Studies" has been revised and now reads as follows:

> [redacted] has been evaluated in 6 clinical trials involving a total of 1165 patients, with 752 receiving [redacted] A loading dose followed by a maintenance infusion was administered to achieve target concentrations of 0.3 or 0.6 ng/mL using continuous infusions of 15 minutes (002, 004, 014, 015, 016, and 021) prior to induction of anesthesia and continued until determination of MAC response (016), the end of surgery (002), 2 hours (014 and 021), 6 hours (004), or 12 hours (015) postoperatively. [redacted] was well tolerated during pre-, intra-, and postoperative administration. However, reports of hypotension have been associated with [redacted] infusion.

We recognize that the Agency has not accepted a brand name for this product and we will update the package insert once that occurs. If you have any additional questions, please do not hesitate to telephone me.

Sincerely,

ABBOTT LABORATORIES

Thomas F. Willer

Thomas F. Willer, Ph.D.
Associate Director, Regulatory Affairs
Hospital Products Division
Phone: (847) 937-6845
Fax: (847) 938-7867
Internet: WILLETF@hpd.abbott.com

TFW:tw

g:9-991.tfw/59

HI - I WILL MAIL A PAPER COPY ON 9/17/99. STAY DRY! TOM

ABBOTT
Hospital Products Division

To: DR S SAMANTA

Company: FDA

FAX #: 301 - 443 - 7068

Date: 9/16/99

No. of Pages: 3 (including cover page)

From: Dr. Tom Willer
Regulatory Affairs

(847) 937-6845 (telephone)
(847) 938-7867 (fax)

Hi - I will also mail a paper copy. Tom

ABBOTT
Hospital Products Division

To: DR S SAMANTA

Company: FDA

FAX #: 301 - 480 - 8682

Date: 9/10/99

No. of Pages: 26 (including cover page)

From: Dr. Tom Willer
Regulatory Affairs

(847) 937-6845 (telephone)
(847) 938-7867 (fax)

ABBOTT

Hospital Products Division
Abbott Laboratories
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200 Abbott Park Road
Abbott Park, Illinois 60064-6157

September 10, 1999

CENTER FOR DRUG EVALUATION AND RESEARCH
ANESTHETIC, CRITICAL CARE & ADDICTION DRUG PRODUCTS, HFD #170
Attn: DOCUMENT CONTROL ROOM #9B-23
5600 Fishers Lane
Rockville, Maryland 20857-1706

ATTENTION: Cynthia McCormick, M.D.
Director

Re: NDA 21-038 Dexmedetomidine Hydrochloride Injection

Abbott Laboratories hereby amends the above-referenced new drug application for the subject drug product. We are responding to a teleconference on September 9, 1999 between FDA : Dr. Patricia. Hartwell and Dr. Susmita Samanta and Abbott Laboratories: Ms. Patricia Scaman, Ms. Rita Tiehen, and Dr. Thomas. Willer. The FDA requested a translated copy of a Case Report Form – Adverse Event Information for Patient No. 9, dated August 9, 1995. We were able to telephone Japan late yesterday and the requested translation was faxed to Abbott today. Please see Exhibit I.

We trust that this submission is complete. If additional information or clarification is needed, please telephone me at your earliest request.

Sincerely,

ABBOTT LABORATORIES

Thomas F. Willer

Thomas F. Willer, Ph.D.
Associate Director, Regulatory Affairs
Hospital Products Division
Phone: (847) 937-6845
Fax: (847) 938-7867
Internet: WILLETF@hpd.abbott.com

TFW:tw

g:9-99f.tfw/36
Attachment

EXHIBIT I

CASE REPORT FORM

ADVERSE EVENT INFORMATION FOR PATIENT NO. 9

DATED AUGUST 9, 1995

APPEARS THIS WAY
ON ORIGINAL

NOTE

WE PROVIDE THE ORIGINAL JAPANESE AE FORM.

THE ENGLISH TRANSLATION HAS BEEN TYPED IN BELOW THE JAPANESE WORDING.

FOR THE CONVENIENCE OF THE AGENCY, SINCE THE TYPE IS RATHER SMALL, WE PROVIDE A TYPED COPY FOLLOWING EACH ORIGINAL PAGE.

3

シーピーシークリニック
CPC Clinic

有害事象 (1)
Adverse Event

治験番号：CPC 95 - 05
Study No.

治験ステージ： Subject Admission — Follow-up Study
Study Period

被験者番号： C 9
Subject No.

Subject Initials

有害事象の有無 1. ☑ 有り Yes 2. ☐ 無し No
Any Adverse Event Observed ?

有りの場合は、以下の欄に記入すること。
If Yes, Complete One Column Per Event.

観察された

[illegible] 8:08 [illegible] 13:30 [illegible]

Drowsiness was observed during the period from 3 minutes (08:08) after the start of study drug dosing till 5 hours and 20 minutes (13:30) after completion of the study drug infusion. The subject was able to open his eyes easily when instructed to verbally but began falling asleep again in the absence of such instructions.

[illegible] (67/27mmHg) [illegible] 0.5mg [illegible] 23 [illegible] 11:22 [illegible]

The subject complained of nausea at the completion of blood sample collection and vital sign monitoring (immediately after removing the used to monitor vital signs), 2 hours 50 minutes (11:00) after completion of the infusion. The subject's posture was changed from semi-supine to one where the upper limbs were allowed to hang vertically with the lower extremities raised. Blood pressure at this time was 67/27mmHg. After i.v. administration of 0.5mg atropine sulfate, blood pressure increased and the nausea disappeared. Bradycardia (minimum 23 bpm) was also observed when the blood pressure decreased, however the subject's pulse rate gradually increased after receiving the atropine sulfate. Blood pressure and pulse rate had almost reverted to baseline values at 11:22.

出現日時 Onset Date	95 年 (yr) 08 時(24hr)	
程度 Grade	1. ☑ 軽度 Slight	Slight Moderate Severe
転帰 Outcome	有害事象持続 Event Continuing 1. ☐ 継続 (Yes) 2. ☑ 消失 (No) ☐ 治験終了時には有害事象消失 Event Resolved at End of Study	有害事象持続 Event Continuing 1. ☐ 継続 (Yes) 2. ☑ 消失 (No) ☐ 治験終了時には有害事象消失 Event Resolved at End of Study
経過 Event Course	持続性 Continuous 1. ☐ Yes 2. ☑ No No の時のエピソードの回数 If No, Number of Episodes 01	持続性 Continuous 1. ☐ Yes 2. ☑ No No の時のエピソードの回数 If No, Number of Episodes 01

治験担当医師：
Physician in Charge [signature]

日付： 1 9 95 年 (yr) 08 月 (mth) 31 日 (dy)
Date

Adverse Event (1)

Study No.:CPC95-05

Subject # 09 Subject Initials: —

Any Adverse Event Observed? Yes

Onset Date: 08:08, 24 August, 1995

Observed Events:
Drowsiness was observed during the period from 8 minutes (08:08) after the start of study drug dosing till 5 hours and 20 minutes (13:30) after completion of the study drug infusion.. The subject was able to open his eyes easily when instructed to verbally but began falling asleep again in the absence of such instructions.

Grade: 1. Slight, Outcome: Event Continuing 2. No

Event Course: Continuous 2. No If No, Number of Episodes 1

Onset Date: 11:05, 24 August, 1995

Event Observed:

The subject complained of nausea at the completion of blood sample collection and vital sign monitoring (immediately after removing the used to monitor vital signs), 2 hours 50 minutes (11:00) after completion of the infusion. The subject's posture was changed from semi-supine to one where the upper limbs were allowed to hang vertically with the lower extremities raised. Blood pressure at this time was 67/27mmHg. After i.v. administration of 0.5mg atropine sulfate, blood pressure increased and the nausea disappeared. Bradycardia (minimum 23 bpm) was also observed when the blood pressure decreased, however the subject's pulse rate gradually increased after receiving the atropine sulfate. Blood pressure and pulse rate had almost reverted to baseline values at 11:22.

Grade: 3. Severe, Outcome: Event Continuing 2. No

Event Course: Continuous 2. No If No, Number of Episodes 1

5

シービーシークリニック　　有害事象（2）
CPC Clinic　　Adverse Event

治験番号：CPC 95 - 05
Study No.

治験ステージ：　Subject Admission
Study Period　　— Follow-up Study

被験者番号：09　　ニシ
Subject No.　　Subject Initials

観察された有害事象 Event Observed	Drowsiness after dosing with the study drug.	Nausea, decreased BP, and bradycardia after dosing with the study drug
有害事象出現最終日時 End Date and Time	95 年(yr) 08 月(mth) 24 日(day) 13 時(24hr) : 30 分(min)	95 年(yr) 08 月(mth) 24 日(day) 11 時(24hr) : 22 分(min)
治験薬との因果関係 Relation to Investigational Drug	1. ☐ 関連なし(Not related) 2. ☐ 関連ないともいえない (Probably not related) 3. ☐ 多分、関連あり (Probably related) 4. ☑ 明らかに関連あり(Related)	1. ☐ 関連なし(Not related) 2. ☐ 関連ないともいえない (Probably not related) 3. ☐ 多分、関連あり (Probably related) 4. ☑ 明らかに関連あり(Related)
投薬前に存在したか Present Before Dosing	1. ☐ はい Yes　2. ☑ いいえ No 3. ☐ 不明 Unknown	1. ☐ はい Yes　2. ☑ いいえ No 3. ☐ 不明 Unknown
投薬の変更 Action Taken on Study Drug Dosage	1. ☑ 投与の継続 None　2. ☐ 投与の減量 Dose Changed 3. ☐ 投与の中止 Drug Withdrawn	1. ☑ 投与の継続 None　2. ☐ 投与の減量 Dose Changed 3. ☐ 投与の中止 Drug Withdrawn
治療の有無 Corrective Therapy	1. ☐ 有 Yes　2. ☑ 無 No	1. ☑ 有 Yes　2. ☐ 無 No

治験担当医師：　　日付：19 95 年(yr) 08 月(mth) 31 日(day)
Physician in Charge　　Date

Onset Date: 13:30, 24 August, 1995

Event Observed:

Drowsiness after dosing with the study drug.

Relationship to Investigational Drug: 4. Related, Present Before Dosing: 2. No

Action Taken on Study Drug Dosage: 1. None, Corrective Therapy: 2. No

Onset Date: 11:22, 24 August, 1995

Event Observed:
Nausea, decreased BP, and bradycardia after dosing with the study drug

Relationship to Investigational Drug: 4. Related, Present Before Dosing: 2. No

Action Taken on the Study Drug Dosing 1. None , Corrective Therapy: 2. Yes

APPEARS THIS WAY
ON ORIGINAL

シービーシークリニック
CPC Clinic

有害事象 (3)
Adverse Event

治験番号：CPC 95 - 05
Study No.

治験ステージ：Subject Admission ~ Follow-up Study
Study Period

被験者番号：09
Subject No.

Subject Initials

観察された有害事象 Event Observed	服薬後の自覚 Drowsiness after dosing with the study drug.	吐き気、血圧低下、徐脈 Nausea, decreased blood pressure, and bradycardia after dosing with the study drug.
有害事象は右記のどれに分類されるか（あてはまるものは全てチェック） Dose The Adverse Event Fall into Any of The Following Categories. Tick More Than One If Necessary.	1. ☐ 死亡 Death	1. ☐ 死亡 Death
	2. ☐ 死亡につながるおそれがある Life-threatening	2. ☐ 死亡につながるおそれがある Life-threatening
	3. ☐ 永久的身体障害 Any event which is permanently disabling	3. ☐ 永久的身体障害 Any event which is permanently disabling
	4. ☐ 入院 Any event which requires or prolongs inpatient hospitalization	4. ☐ 入院 Any event which requires or prolongs inpatient hospitalization
	5. ☐ 発癌 Case of Carcinogenesis	5. ☐ 発癌 Case of Carcinogenesis
	6. ☐ 先天性異常 Congenital abnomaly	6. ☐ 先天性異常 Congenital abnomaly
	7. ☐ 過量投与 Overdose of the test drug	7. ☐ 過量投与 Overdose of the test drug
	8. ☑ その他 Other	8. ☑ その他 Other

治験担当医師：
Physician in Charge

日付：Date 19 95 年(yr) 05 月(mth) 31 日(day)

8

Event Observed:

Drowsiness after dosing with the study drug.

Does the adverse event fall into any of the following categories? Pick more than one if necessary.: 8. Others

Event Observed:

Nausea, decreased blood pressure, and bradycardia after dosing with the study drug.

Does the adverse event fall into any of the following categories? Pick more than one if necessary.: 8. Others

APPEARS THIS WAY
ON ORIGINAL

9

シービーシークリニック
CPC Clinic

有害事象（4）
Adverse Event

治験番号：CPC 95 - 05
Study No.

治験ステージ：
Study Period

Subject Admission
— Follow-up Study

被験者番号：09
Subject No.

Subject Initials

観察された有害事象 Event Observed	Drowsiness after dosing with the study drug.	Nausea, decreased BP, and bradycardia after dosing with the study drug.
安全性に対する総合評価 (General comment on safety)	1：☑ 問題なし (No problem) 2：☐ やや問題あり (Slightly problematic) 3：☐ かなり問題あり (Pretty probiematic) 4：☐ 非常に問題あり (Very problematic)	1：☐ 問題なし (No problem) 2：☑ やや問題あり (Slightly problematic) 3：☐ かなり問題あり (Pretty probiematic) 4：☐ 非常に問題あり (Very problematic)

有害事象に関する治験担当医師のコメント (Comment of physician in charge)
傾眠に関しては薬理作用（鎮静効果）に基づく事象と推定され予想外の有害事象ではない事、程度も軽い事、より安全性に問題なしと判断した。
悪心、血圧低下、徐脈は薬の薬理作用に基づく事象であり予想外の有害事象ではない事、アトロピン等の拮抗薬により迅速な回復が認められる事より大きな問題は生じないと考えられるが、緊急時に備えた設備、薬物を備えた環境で投与する必要がある！！より安全性は若干問題ありと判断する。

Comments from physician (investigator) at site:
Drowsiness was to be expected event based the known pharmacological effect (sedative effect of DEX) and its intensity is mild (Mild drowsiness is an expected event given the known pharmacological effect of this drug (sedative effect of DEX)). Thus this event was not judged as to be clinically meaningful in terms of safety.

Nausea, decreased BP and bradycardia were also all expected events given the known pharmacological effect of DEX. Since these events were temporary and quickly reversed with relevant treatment (such as atropin injection, an anti-cholinergic agent), there were no serious outcome. However in the case of an emergency requiring medical intervention, sufficient equipment and drugs should be available where DEX is used. Therefore these events were judged as somewhat clinically significant in terms of safety.

治験担当医師：
Physician in Charge

日付：Date　19 95 年(yr)　08 月(mth)　31 日(day)

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Event Observed:

Drowsiness after dosing with the study drug.

General comment (Global assessment) on safety : No problems

Event Observed:

Nausea, decreased BP, and bradycardia after dosing with the study drug.

General comment (Global assessment) on safety : Slightly problematic

Comments from physician (investigator) at site:

Drowsiness was to be expected event based the known pharmacological effect (sedative effect of DEX) and its intensity is mild. (Mild drowsiness is an expected event given the known pharmacological effect of this drug (sedative effect of DEX)) Thus this event was judged not to be clinically meaningful in terms of safety.

Nausea, decreased BP and bradycardia were also all expected events given the known pharmacological effect of DEX. Since these events were temporary and quickly reversed with relevant treatment • such as atropin injection, an anti-chorinergic agent), there were no serious outcome. However in the case of an emergency requiring medical intervention, sufficient equipment and drugs should be available where DEX is used. Therefore these events were judged as somewhat clinically significant in terms of safety.

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シーピーシークリニック
CPC Clinic

有害事象2(1)
Adverse Event

治験番号：CPC 95 - 05
Study No.

治験ステージ：Subject Admission ~ Follow-up Study
Study Period

被験者番号：C 9
Subject No.

Subject Initials

有害事象の有無 Any Adverse Event Observed ?	1. ☑ 有り Yes	2. ☐ 無し No

有りの場合は、以下の欄に記入すること。
If Yes, Complete One Column Per Event.

観察された有害事象 Event Observed	[illegible handwritten Japanese]	[illegible handwritten Japanese]
出現日時 Onset Date	95 年 (yr) 0 月 ... 14 : 4 時(24hr) 分(min)	時(24hr) 分(min)
		1. ☑ 軽度 Slight 2. ☐ 中等度 Moderate 3. ☐ 高度 Severe
		有害事象持続 Event Continuing
転帰 Outcome	1. ☐ 継続 (Yes) 2. ☑ 消失 (No) ☐ 治験終了時には有害事象消失 Event Resolved at End of Study	1. ☐ 継続 (Yes) 2. ☑ 消失 (No) ☐ 治験終了時には有害事象消失 Event Resolved at End of Study
経過 Event Course	持続性 Continuous 1. ☐ Yes 2. ☑ No; Noの時のエピソードの回数 If No, Number of Episodes: 0 1	持続性 Continuous 1. ☐ Yes 2. ☑ No; Noの時のエピソードの回数 If No, Number of Episodes: 0 1

During blood sample collection at 11:00, atrioventricular junctional rhythm was observed on the ECG while monitoring the subject for bradycardia. The ECG after lunch showed that this event had resolved.

After lunch, two episodes of single ventricular extrasystole were observed in the ECG (14:47, 14:49). These events occurred when the subject was walking up and down the stairs between the 2nd and 3rd floors. The subject has intended to go to the lounge on the 3rd floor and returned to the ECG monitoring room at the onset of the event. The heart rate was 75 to 76 bpm; ECG was continuously monitored until 16:00. No further episodes of ventricular extrasystole or arrhythmia were observed.

治験担当医師：[signature]
Physician in Charge

日付：19 95 年 (yr) 03 月 (mth) 31 日 (day)
Date

Onset Date: 14:47, 24 August, 1995

Event Observed:

After lunch, two episodes of single ventricular extrasystole were observed in the ECG (14:47, 14:49). These events occurred when the subject was walking up and down the stairs between the 2nd and 3rd floors. The subject has intended to go to the lounge on the 3rd floor and returned to the ECG monitoring room at the onset of the event. The heart rate was 75 to 76 bpm; ECG was continuously monitored until 16:00. No further episodes of ventricular extrasytole or arrhythmia were observed.

Grade: 1. Slight, Outcome: Event Continuing 2. No

Event Course: Continuous 2. No If No, Number of Episodes 1

Onset Date: 11:13, 24 August, 1995

Event Observed:

During blood sample collection at 11:00, atrioventricular junctional rhythm was observed on the ECG while monitoring the subject for bradycardia. The ECG after lunch showed that this event had resolved.

Grade: 1. Slight, Outcome: Event Continuing 2. No

Event Course: Continuous 2. No If No, Number of Episodes 1

シービーシークリニック
CPC Clinic

有害事象(2)
Adverse Event

治験番号：CPC 95 - 05
Study No.

治験ステージ：
Study Period

Subject Admission
~ Follow-up Study

被験者番号：09
Subject No.

Subject Initials

観察された有害事象 Event Observed	Ventricular extrasystole	Atrioventricular junctional rhythm
有害事象出現/終了日時 End Date and Time	95 年(yr) 08 月(mth) 24 日(day) 14 時(24hr) : 49 分(min)	95 年(yr) 08 月(mth) 24 日(day) 14 時(24hr) : 47 分(min)
治験薬との因果関係 Relation to Investigational Drug	1. ☐ 関連なし(Not related) 2. ☑ 関連ないともいえない (Probably not related) 3. ☐ 多分、関連あり (Probably related) 4. ☐ 明らかに関連あり(Related)	1. ☐ 関連なし(Not related) 2. ☐ 関連ないともいえない (Probably not related) 3. ☐ 多分、関連あり (Probably related) 4. ☑ 明らかに関連あり(Related)
投薬前に存在したか Present Before Dosing	1. ☐ はい Yes 2. ☑ いいえ No 3. ☐ 不明 Unknown	1. ☐ はい Yes 2. ☑ いいえ No 3. ☐ 不明 Unknown
投薬の変更 Action Taken on Study Drug Dosage	1. ☑ 投与の継続 None 2. ☐ 投与の減量 Dose Changed 3. ☐ 投与の中止 Drug Withdrawn	1. ☑ 投与の継続 None 2. ☐ 投与の減量 Dose Changed 3. ☐ 投与の中止 Drug Withdrawn
治療の有無 Corrective Therapy	1. ☐ 有 Yes 2. ☑ 無 No	1. ☑ 有 Yes 2. ☐ 無 No

治験担当医師：
Physician in Charge

日付：19 95 年(yr) 08 月(mth) 31 日(day)
Date

End Date and Time: 14:49, 24 August, 1995

Event Observed:

Ventricular extrasystole

Causality: Probably not related Present Before Dosing: No

Action taken on study drug dosing: None Corrective Therapy (Medical intervention):

No

End Date and Time: 14:47, 24 August, 1995

Event Observed:

Atrioventricular junctional rhythm

Causality: Related , Present before Dosing: No

Action taken on study drug dosing: None Corrective Therapy (Medical intervention):

Yes

シービーシークリニック
CPC Clinic

有害事象2(3)
Adverse Event

治験番号：CPC 95 - 05
Study No.

治験ステージ：
Study Period

Subject Admission
～ Follow-up Study

被験者番号：09
Subject No.

Subject Initials

観察された有害事象 Event Observed	Ventricular extrasystole	Atrioventricular junctional rhythm
有害事象は右記のどれに分類されるか（あてはまるものは全てチェック） Dose The Adverse Event Fall into Any of The Following Categories . Tick More Than One If Necessary .	1. ☐ 死亡 Death 2. ☐ 死亡につながるおそれがある Life-threatening 3. ☐ 永久的身体障害 Any event which is permanently disabling 4. ☐ 入院 Any event which requires or prolongs inpatient hospitalization 5. ☐ 発癌 Case of Carcinogenesis 6. ☐ 先天性異常 Congenital abnomaly 7. ☐ 過量投与 Overdose of the test drug 8. ☑ その他 Other	1. ☐ 死亡 Death 2. ☐ 死亡につながるおそれがある Life-threatening 3. ☐ 永久的身体障害 Any event which is permanently disabling 4. ☐ 入院 Any event which requires or prolongs inpatient hospitalization 5. ☐ 発癌 Case of Carcinogenesis 6. ☐ 先天性異常 Congenital abnomaly 7. ☐ 過量投与 Overdose of the test drug 8. ☑ その他 Other

治験担当医師：
Physician in Charge

日付：
Date

19 95 年 (yr) 08 月 (mth) 31 日 (day)

16

Event Observed:

Ventricular extrasystole

Does the adverse event fall into any of the following categories? Pick more than one if necessary.: 8. Others

Event Observed:

Atrioventricular junctional rhyme

Does the adverse event fall into any of the following categories? Pick more than one if necessary.: 8. Others

APPEARS THIS WAY
ON ORIGINAL

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シービーシークリニック
CPC Clinic

有害事象シート(4)
Adverse Event

治験番号：CPC 95 - 05
Study No.

治験ステージ：
Study Period

Subject Admission
～ Follow-up Study

被験者番号：09
Subject No.

Subject Initials

観察された有害事象 Event Observed	Ventricular extrasystole	Atrioventricular junctional rhythm
安全性に対する総合評価 (General comment on safety)	1：☑ 問題なし (No problem) 2：☐ やや問題あり (Slightly problematic) 3：☐ かなり問題あり (Pretty probiematic) 4：☐ 非常に問題あり (Very problematic)	1：☑ 問題なし (No problem) 2：☐ やや問題あり (Slightly problematic) 3：☐ かなり問題あり (Pretty probiematic) 4：☐ 非常に問題あり (Very problematic)

有害事象に関する治験担当医師のコメント (Comment of physician in charge)

Comments from physician (investigator) at site:

There was a long period between the onset of ventricular extrasystole and Dex dosing (about 3 hrs after dosing). Results from non-clinical studies and overseas clinical studies did not report any association between arrhythmia and DEX properties. Ventricular extrasystole was also not reported in studies with clonodine, a compound similar to DEX. Therefore this event is not likely to be a DEX related event. In addition to this, ventricular extrasystole is sometimes observed even in healthy subjects. In cardiac impairment cases where no organopathy is indicated in his basic condition, this event is not considered to be clinically meaningful. Thus based on the above, this event was more judged as clinically significant in terms of safety.

With respect to atrioventricular junctional rhythm, this event is sometimes observed even in healthy subjects who are vagotonic. In cardiac impairment cases where no organopathy is indicated in the his basic condition, this event is not considered to be clinically meaningful. Thus based on the above, this event was judged not to be clinically significant in terms of safety.

治験担当医師：
Physician in Charge

日付：19 95 08 31
Date 年 (yr) 月 (mth) 日 (day)

18

Event Observed:

Ventricular extrasystole

~~General comment (Global assessment) on safety : No problems~~

Event Observed:

Atrioventricular junctional rhythm

General comment (Global assessment) on safety : No problems

Comments from physician (investigator) at site:

There was a long period between the onset of ventricular extrasystole and Dex dosing (about 3.5hrs after dosing). Results from non-clinical studies and overseas clinical studies did not report any association between arrhythmia and DEX properties. Ventricular extrasystole was also not reported in studies with clonodine, a compound similar to DEX. Therefore this event is not likely to be a DEX related event. In addition to this, ventricular extrasystole is sometimes observed even in healthy subjects. In cardiac impairment cases where no organopathy is indicated in his basic condition, this event is not considered to be clinically meaningful. Thus based on the above, this event was judged not to be clinically significant in terms of safety.

With respect to atrioventricular junctional rhythm, this event is sometimes observed even in healthy subjects who are vagotonic. In cardiac impairment cases where no organopathy is indicated in the his basic condition, this event is not considered to be clinically meaningful. Thus based on the above, this event was judged not to be clinically significant in terms of safety.

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シービーシークリニック
CPC Clinic

有害事象3(1)
Adverse Event

治験番号：CPC 95-05
Study No.

治験ステージ：Subject Admission ~ Follow-up Study
Study Period

被験者番号：09
Subject No.

Subject Initials

有害事象の有無 Any Adverse Event Observed ? 1. [✓] 有り Yes 2. [ ] 無し No

有りの場合は、以下の個に記入すること。
If Yes, Complete One Column Per Event.

観察された有害事象 Event Observed	投与24時間後検査にて投与前値に比べ赤血球、ヘモグロビン値の低下を認めた。最低値は投与後1週間に最低値となり、投与後11日目には上昇を示した Decreases in RBC and Hb were observed 24 hrs after dosing with the study drug. Both RBC and Hb reached minimum values 1 week after dosing. At 11 days after dosing both values had increased.	Decrease in RBC and Hb observed 24hrs after dosing. Both RBC and Hb reached minimum value 1 week after dosing. Increased 11 days after dosing.
出現日時 Onset Date	95 年(yr) 08 月(mth) 25 日(day) 08 時(24hr) : 00 分(min)	年(yr) 月(mth) 日(day) 時(24hr) : 分(min)
程度 Grade	1. [✓] 軽度 Slight 2. [ ] 中等度 Moderate 3. [ ] 高度 Severe	1. [ ] 軽度 Slight 2. [ ] 中等度 Moderate 3. [ ] 高度 Severe
転帰 Outcome	有害事象持続 Event Continuing 1. [ ] 継続 (Yes) 2. [✓] 消失 (No) [ ] 治験終了時には有害事象消失 Event Resolved at End of Study	有害事象持続 Event Continuing 1. [ ] 継続 (Yes) 2. [ ] 消失 (No) [ ] 治験終了時には有害事象消失 Event Resolved at End of Study
経過 Event Course	持続性 Continuous 1. [ ] Yes 2. [✓] No No の時のエピソードの回数 If No, Number of Episodes 01	持続性 Continuous 1. [ ] Yes 2. [ ] No No の時のエピソードの回数 If No, Number of Episodes

治験担当医師：
Physician in Charge

日付：19 95 年(yr) 11 月(mth) 10 日(day)
Date

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Onset Date: 08:00, 25 August, 1995

Observed Events:

Decreases in RBC and Hb were observed 24 hrs after dosing with the study drug. Both RBC and Hb reached minimum values 1 week after dosing. At 11 days after dosing both values had increased.

Grade: 1. Slight, Outcome: Event Continuing 2. No

Event Course: Continuous 2. No If No, Number of Episodes 1

シービーシークリニック
CPC Clinic

有害事象3(2)
Adverse Event

治験番号：CPC 95-05
Study No.

治験ステージ：
Study Period
Subject Admission ～ Follow-up Study

被験者番号：09
Subject No.

被験
Subject Initials

観察された有害事象 Event Observed	投薬後の赤血球、ヘマトクリット値の減少 Decreased in RBC and Hb	
有害事象出現/終了日時 End Date-and Time	95 年(yr) 09 月(mth) 04 日(day) 12 時(24hr) : 00 分(min)	年(yr) 月(mth) 日(day) 時(24hr) : 分(min)
治験薬との因果関係 Relation to Investigational Drug	1. ☐ 関連なし(Not related) 2. ☑ 関連ないともいえない (Probably not related) 3. ☐ 多分、関連あり (Probably related) 4. ☐ 明らかに関連あり(Related)	1. ☐ 関連なし(Not related) 2. ☐ 関連ないともいえない (Probably not related) 3. ☐ 多分、関連あり (Probably related) 4. ☐ 明らかに関連あり(Related)
投薬前に存在したか Present Before Dosing	1. ☐ はい Yes 2. ☑ いいえ No 3. ☐ 不明 Unknown	1. ☐ はい Yes 2. ☐ いいえ No 3. ☐ 不明 Unknown
投薬の変更 Action Taken on Study Drug Dosage	1. ☑ 投与の継続 None 2. ☐ 投与の減量 Dose Changed 3. ☐ 投与の中止 Drug Withdrawn	1. ☐ 投与の継続 None 2. ☐ 投与の減量 Dose Changed 3. ☐ 投与の中止 Drug Withdrawn
治療の有無 Corrective Therapy	1. ☐ 有 Yes 2. ☑ 無 No	1. ☐ 有 Yes 2. ☐ 無 No

治験担当医師：
Physician in Charge

日付：19 95 年(yr) 11 月(mth) 10 日(day)
Date

22

End Date and Time: 12:00, 4 September, 1995

Event observed:

Decreases in RBC and Hb

Causality: Probably not related Present Before Dosing: No

Action taken on sthdy drug dosing: None Corrective Therapy (Medical intervention):

No

シーピーシークリニック
CPC Clinic

有害事象3(3)
Adverse Event

治験番号：CPC 95 - 05
Study No.

治験ステージ：Subject Admission
Study Period — Follow-up Study

被験者番号：0 9
Subject No.

Subject Initials

観察された有害事象 Event Observed	[illegible] Decreases in RBC and Hb	
有害事象は右記のどれに分類されるか（あてはまるものは全てチェック） Dose The Adverse Event Fall into Any of The Following Categories. Tick More Than One If Necessary.	1. ☐ 死亡 Death	1. ☐ 死亡 Death
	2. ☐ 死亡につながるおそれがある Life-threatening	2. ☐ 死亡につながるおそれがある Life-threatening
	3. ☐ 永久的身体障害 Any event which is permanently disabling	3. ☐ 永久的身体障害 Any event which is permanently disabling
	4. ☐ 入院 Any event which requires or prolongs inpatient hospitalization	4. ☐ 入院 Any event which requires or prolongs inpatient hospitalization
	5. ☐ 発癌 Case of Carcinogenesis	5. ☐ 発癌 Case of Carcinogenesis
	6. ☐ 先天性異常 Congenital abnomaly	6. ☐ 先天性異常 Congenital abnomaly
	7. ☐ 過量投与 Overdose of the test drug	7. ☐ 過量投与 Overdose of the test drug
	8. ☑ その他 Other	8. ☐ その他 Other

治験担当医師：[signature]
Physician in Charge

日付：19 95 年 (yr) 11 月 (mth) 10 日 (day)
Date

24

Event observed:

Decreases in RBC and Hb

Does the adverse event fall into any of the following categories? Pick more than one if necessary.: 8. Others

APPEARS THIS WAY
ON ORIGINAL

シービーシークリニック
CPC Clinic

有害事象3(4)
Adverse Event

治験番号：CPC 95-05
Study No.

治験ステージ：Subject Admission
Study Period ～ Follow-up Study

被験者番号：09
Subject No.　　Subject Initials

観察された有害事象 Event Observed	投与後の赤血球, 血色素減少 Decreases in RBC and Hb	
安全性に対する総合評価 (General comment on safety)	1：☑ 問題なし (No problem) 2：☐ やや問題あり (Slightly problematic) 3：☐ かなり問題あり (Pretty probiematic) 4：☐ 非常に問題あり (Very problematic)	1：☐ 問題なし (No problem) 2：☐ やや問題あり (Slightly problematic) 3：☐ かなり問題あり (Pretty probiematic) 4：☐ 非常に問題あり (Very problematic)

有害事象に関する治験担当医師のコメント (Comment of physician in charge)
治験薬との因果関係は完全には否定できないが、赤血球、ヘモグロビン減少の原因としては採血量の増加による採血貧血が最も考えられること、程度は軽く貧血による症状も認められなかったことより安全性は問題なしと判断した。

Comments from physician (investigator) at site:
Though these events were not judged as 'completely not related', these decreases in RBC and Hb can most likely be attributed to the relatively large blood sampling volume. These decreases were mild, and no conditions related to anemia were observed. Therefore, these events were judged not to be clinically significant in terms of safety.

治験担当医師：
Physician in Charge

日付：19 95 (年 yr) 11 (月 mth) 10 (日 day)
Date

26

Event Observed:

Decreases in RBC and Hb

General comment (Global assessment) on safety : No problems

Comments from physician (investigator) at site:

Though these events were not judged as 'completely not related', these decreases in RBC and Hb can most likely be attributed to the relatively large blood sampling volume. These decreases were mild, and no conditions related to anemia were observed. Therefore, these events were judged not to be clinically significant in terms of safety.

ABBOTT
Hospital Products Division

To: DR S SAMANTA

Company: FDA

FAX #: 301-480-8682

Date: 9/10/99

No. of Pages: 2 (including cover page)

From: Dr. Tom Willer
Regulatory Affairs

(847) 937-6845 (telephone)
(847) 938-7867 (fax)

ABBOTT

Hospital Products Division
Abbott Laboratories
D-389, Bldg. AP30
200 Abbott Park Road
Abbott Park, Illinois 60064-6157

September 9, 1999

CENTER FOR DRUG EVALUATION AND RESEARCH
ANESTHETIC, CRITICAL CARE & ADDICTION DRUG PRODUCTS, HFD #170
Attn: DOCUMENT CONTROL ROOM #9B-23
5600 Fishers Lane
Rockville, Maryland 20857-1706

ATTENTION: Dr. Susmita Samanta, M.D. FAX 301-480-8682
Project manager

Re: Request for Guidance - Stability

Regarding NDA 21-038 [redacted] xmedetomidine HCl) for Infusion, Abbott Laboratories would like to submit a new container size, [redacted] s vial, after this NDA is approved. We are making plans now to put this proposed new size on stability. [redacted]. It is the same product formulation. There are no changes in the manufacturing procedures, manufacturing site, et al. The only changes are the larger size vial and fill volume. We currently have under Agency review a [redacted] al.

In support [redacted] ss vial supplement, we propose submitting three lots of product placed on three months accelerated stability at 40°C/75% RH. We would do testing at zero, one, two, and three months. We will test for: physical appearance, color, particulate matter, sterility, BET, dexmedetomidine assay, optical purity, related substances, pH, sodium chloride. This testing conforms to the previously submitted marketed product stability protocol in terms of the terms to be performed.

Please contact me at your earliest convenience with comments and/or approval of our proposed stability plan for the [redacted]

Sincerely,

ABBOTT LABORATORIES

Thomas F. Willer

Thomas F. Willer, Ph.D.
Associate Director, Regulatory Affairs
Hospital Products Division
Phone: (847) 937-6845
Fax: (847) 938-7867
Internet: WILLETF@hpd.abbott.com

TFW:tw

ABBOTT

Hospital Products Division
Abbott Laboratories
D-389, Bldg. AP30
200 Abbott Park Road
Abbott Park, Illinois 60064-6157

September 2, 1999

CENTER FOR DRUG EVALUATION AND RESEARCH
ANESTHETIC, CRITICAL CARE & ADDICTION DRUG PRODUCTS, HFD #170
Attn: DOCUMENT CONTROL ROOM #9B-23
5600 Fishers Lane
Rockville, Maryland 20857-1706

ATTENTION: Cynthia McCormick, M.D.
Director

Re: NDA 21-038 [redacted] (dexmedetomidine HCl) for Infusion

Abbott Laboratories hereby amends the above-referenced new drug application for the subject drug product. The FDA and Abbott Laboratories conducted a teleconference on September 1, 1999. Participating for the FDA were the following individuals: Dr. C. McCromick, Division Director; Dr. R. Rapapport, Assistant Division Director; Dr. P. Hartwell, Medical Reviewer; and Dr. S. Samanta, Project Manager. Participating for Abbott Laboratories were Dr. M. Etropolski, Medical Director; Ms. J. Sayre, Senior Operations Manager; and Dr. T. Willer, Associate Director, Regulatory Affairs. The Agency requested several items of safety data: (1) case report forms (CRFs) for three patients who died in studies 3005006 [redacted] W98-263 (Abbott) and W98-264 (Abbott), (2) information and CRFs regarding three subjects in the Japanese Phase I study (J-DEX-9501) who experienced hematological changes, (3) CRF for subject #9 in Japanese Phase I study (J-DEX-9501) who experienced an SAE, (4) an explanation of why the [redacted] and Japanese studies were not included in the Integrated Summary of Safety in the NDA, (5) breakdown of adverse incidences by study for the ISS Supplement, including [redacted] and Japanese studies.

To comply with request number 1, please find enclosed as Exhibit I case report forms for the following: [redacted] study 3005006, patient #211; Abbott study W98-263, patient #104; and Abbott study W98-264, patient #101.

Please find enclosed as Exhibit II selected pages from the J-DEX-9501 final clinical report Appendix and the case report forms for the three subjects who experienced hematological changes.

In the Phase I Japanese trial (J-DEX-9501), dexmedetomidine was infused intravenously for 10 minutes at doses of 0.1, 0.3, and 0.6 mcg/kg to 9 healthy Japanese male, adult volunteers. There were no SAEs or AEs leading to discontinuation and none of the subjects died. Although not reported originally as a serious adverse event by the investigator, one subject (#9) experienced bradycardia, hypotension, atrioventricular rhythm, ventricular extrasystole, and nausea during administration of dexmedetomidine 0.6 mcg/kg that resolved after IV injection of atropine sulfate. Notation of this event appeared in the original ISS (Volume 301 of 726, 8/10-239-121) contained in NDA 21-038 (filed December 18, 1998). Subject #9 was also reported by Abbott Laboratories as a Serious Adverse Event (PCA #9902934).

The Japanese J-DEX-9501 final report stated the following regarding hematological changes: "Hematology showed a tendency of slight decreases in RBC and hemoglobin value in one subject (#1) of the 0.1 mcg/kg group and all subjects of the 0.3 and 0.6 mcg/kg groups. These changes might be attributed to blood collection in a relatively large volume specified in this study, but the involvement of the test drug cannot be completely ruled out. Therefore, the causal relationship with the drug was judged as 'possibly related'." In addition, it should be noted that red blood cell counts and hemoglobin values, although reduced, are within normal ranges at 24 hours after study drug administration in the 0.6 mcg/kg group (with the exception of subject #9 who had an RBC of 431 – normal range =438 to 577 x 10,000/mcl), and are therefore not considered clinically significant. Additionally, the changes in this group were in the range of 4% to 8% for the first 24 hours evaluation as compared to the 0.1 mcg/kg group where changes in RBCs measured 5% to 11%.

Please find enclosed as Exhibit III selected pages from the J-DEX-9502 final clinical report Appendix.

In the Phase II trial (J-DEX-9502), dexmedetomidine was infused intravenously for 5 minutes at doses of 0.2, 04, 0.6 and 0.8 mcg/kg to 139 Japanese patients undergoing surgical procedures under inhalation anesthesia. No SAEs were reported during the conduct of this perioperative study. There were no SAEs or AEs leading to discontinuation; none of the subjects died as referenced in the original ISS (Volume 301 of 726, 8/10-239-121) contained in NDA 21-038 (filed December 18, 1998).

Abbott Laboratories is most appreciative of the opportunity to work with the FDA via teleconferences. We are rapidly working to assemble the additional requested information in response to FDA Questions No. 3-5 above, which should be available in the immediate future.

If you have any additional questions, please do not hesitate to contact me.

ABBOTT LABORATORIES

Thomas F. Willer

Thomas F. Willer, Ph.D.
Associate Director, Regulatory Affairs
Hospital Products Division
Phone: (847) 937-6845
Fax: (847) 938-7867
Internet: WILLETF@hpd.abbott.com

TFW:tw

g:9-99f.tfw/17
Attachment

ABBOTT
Hospital Products Division

Hi - paper copy will be fed ex. night. Thurs. Tom

To: Dr S Samanta

Company: FDA

FAX #: 301-480-8682

Date: 9/2

No. of Pages: 3 (including cover page)

From: Dr. Tom Willer
Regulatory Affairs

(847) 937-6845 (telephone)
(847) 938-7867 (fax)

MEETING MINUTES

MEETING DATE: December 1, 1999

Division of Anesthetics, Critical Care and Addiction Drug Products (HFD-170)

NDA 21-038
DRUG: dexmedetomadine HCl
Proposed Indication: Short-term (24 hours or less) ICU sedation in patients 18 years of age and older.

SPONSOR/APPLICANT: Abbott Laboratories

TYPE of MEETING: Briefing meeting for Dr. Jenkins including discussion of pre-approval safety issues

ODE II PARTICIPANTS:
John Jenkins, Director

REVIEW DIVISION PARTICIPANTS:
Suresh Doddapeneni, Biopharm Reviewer
A. D'Sa, CMC Team Leader
Harry Geyer, Pharm/Tox reviewer
Belinda Hayes, Pharm/Tox reviewer
Lucy Jean, Pharm/Tox Team Leader
Mike Klein, CSET Teram Leader
Jonathan Ma, Biostatistical Reviewer
Cynthia McCormick, Director
Tom, Permutt, Biostatistical Team Leader
Bob Rappaport, Deputy Director
Susmita Samanta, PM
Cathie Schumaker, CPMS
Ramana Uppoor, Biopharm Team Leader

OPDRA PARTICIPANTS:
Mary Dempsey, PM
Carol Pamer, Safety Evaluator

DDMAC PARTICIPANTS:
Mark Askine, DDMAC reviewer

MEETING OBJECTIVES:

To provide a routine, formal mechanism for communications between the Office of Drug Evaluation (ODE) review divisions and the Office of Post-Marketing Drug Risk Assessment (OPDRA) risk evaluation divisions prior to the approval of a new chemical entity (NCE) or certain other applications in order to:

(1) Ensure that OPDRA is aware of potential post-marketing safety problems of drugs about to be approved,

(2) Consider, jointly, the need for any special post-marketing analyses or post-marketing safety studies or other evaluations to be implemented by or agreed to by the sponsor prior to the approval of a drug product, and

(3) Determine if there is any special information or feedback that the ODE review division would like from the OPDRA risk evaluation division during the immediate post-launch life of the soon-to-be-approved drug product.

Each discipline presented an overview of the data base reviewed for this NDA.

The safety data base indicates that hypertension, hypotension, and bradycardia are the most common adverse events. Multi-organ failure as a result of the cardiac effects would be the signal that the division would be most interested in having OPDRA monitor. Other signals that are important include: potential for diversion and abuse, liver toxicity with prolonged infusion, and adrenal suppression with long term infusion. Phase 4 commitments will be solicited regarding the long-tem infusion and adrenal suppression issues.

The trade name for this product has not been approved. Abbott has provided an argument for Precedex ——— . The consult regarding nomenclature is being reviewed by OPDRA.

ACTION ITEMS:

Carol Pamer will provide final consult on the nomenclature issue.

/S/

Cathie Schumaker

cc:
Original NDA 21-038
HFD-170/Div File
HFD-170/Attendees
HFD-(430/440)/Division Director
/Deputy Director
/Safety Evaluator
/Safety Evaluator Team Leader
/Epidemiologist
/Project Manager
HFD-042/MAskine

MEETING MINUTES – Briefing/Pre-Approval Safety Conference

APPEARS THIS WAY
ON ORIGINAL

Clinical Pharmacology and Biopharmaceutics Review

NDA: 21-038
Name: [redacted] (Dexmedetomidine HCL) [redacted]
Sponsor: Abbott Laboratories, 200 Abbott Park, Abbott Park, IL 60064
Submission Type: Original NDA
Submission Date: December 18, 1998
Reviewer: Suresh Doddapaneni, Ph.D.

45-Day Filing Review

Abbott Laboratories submitted NDA 21-038 seeking marketing approval for [redacted] (Dexmedetomidine HCL for Infusion) for continuous intravenous infusion use in intensive care setting for providing sedation and analgesia. It is a sterile, non pyrogenic solution suitable for intravenous infusion following dilution. Dexmedetomidine HCL is not approved for marketing in any other country.

Overall, following information pertinent to this indication was provided in the Human Pharmacokinetics and Bioavailability section of NDA 21-038;

[redacted]

2. **Protein binding:**
   Dexmedetomidine is 89 to 92% bound to plasma proteins.
3. **Metabolic inversion:**
   Chiral inversion of dexmedetomidine to its inactive levo-enantiomer is minimal (LOQ of 0.02 ng/mL).
4. **Metabolic Pathways:**
   The metabolic pathways for dexmedetomidine were described. Roughly 62% of the $AUC_{0\text{-}24\ h}$ radioactivity was comprised of N- glucuronides of dexmedetomidine (G-Dex-1 and G-Dex-2), N-Methyl-O-glucuronide, O-glucuronide. Another 15% of the $AUC_{0\text{-}24\ h}$ radioactivity was accounted for by parent drug. The H-3 metabolite, the result of hydroxylation at the methyl position on the methylene bridge, accounted for another 11% of the $AUC_{0\text{-}24\ h}$ radioactivity. In vitro metabolism studies showed that the formation of the OH and H-3 metabolites is mediated largely by CYP2A6, although other CYP forms (1A2, 2E1, 2D6, and 2C19) may also be involved.
5. **Mass Balance:**
   Approximately 85% of the radioactivity was excreted within 24 hours (studies BA-91-04 & DEX-96-018). Approximately 3% of the dosed radioactivity was excreted in the feces while the rest was excreted in the urine as metabolites (no unchanged drug was excreted in the urine).
6. **Dose-Proportionality:**
   Dexmedetomidine clearance is approximately constant within the anticipated therapeutic range, resulting in dose-proportionality. This includes steady state drug plasma

concentrations expected to result from maintenance infusions of up to 0.7 μg/kg/hour (upper limit of maintenance infusion stated in the dosage and administration section of the package insert).

7. **Renal Impairment:**
   Dexmedetomidine pharmacokinetics were not different in the two groups of severe renal impairment subjects and normal healthy subjects studied (study DEX-95-008).
8. **Hepatic Impairment:**
   The mean clearance values for subjects with mild, moderate, and severe hepatic impairment were 74%, 64%, and 53% of those observed in the normal healthy subjects (study DEX-95-009).
9. **Age assessment:**
   Dexmedetomidine pharmacokinetics were not different between young (18 to 40 years), middle-age (41-65 years), and elderly (>65 years) groups (study DEX-96-013).
10. **Gender assessment:**
    Dexmedetomidine pharmacokinetics were not different between male and female subjects in the age assessment study (study DEX-96-013).
11. **Drug-Drug Interactions:**
    No clinically relevant *in vivo* pharmacokinetic drug-drug interactions were reported between dexmedetomidine and midazolam (DEX-95-005), dexmedetomidine and propofol (DEX-96-019), and dexmedetomidine and alfentanil (DEX-95-011).
12. **Analytical Methodology:**

    [redacted]

13. **Package Insert:**
    The pharmacokinetics section of the package insert is annotated and contains the usual information on the ADME aspects of dexmedetomidine and pharmacokinetics of dexemedetomidine in special populations.

Recommendation

A cursory review of New Drug Application 21-038 did not reveal any obvious deficiencies that would preclude its filing. Therefore, NDA 21-038 can be filed from the viewpoint of Office of Clinical Pharmacology and Biopharmaceutics.

/S/

Suresh Doddapaneni, Ph.D.
Clinical Pharmacologist
DPE II/OCPB

FT initialed by John Hunt /S/

CC:
NDA 21-038, HFD-170 (Division File, Morgan), HFD-850 (Lesko), HFD-870 (Doddapaneni, Mei-Ling Chen, Hunt, Uppoor), Barbara Murphy (CDR).

Filing Meeting February 3, 1999 (10:00 a.m. 11:30 a.m.)

NDA: 21-038 ———

Sponsor: Abbott Laboratories
Drug: ——— (dexmedetomidine HCl) ———

Indication: Provides for sedation in the adult ICU setting.

FILEABILITY:

On initial overview of the NDA application:	YES	NO

PHARMACOLOGY:

1. On its face, is the pharmacology section of the NDA organized in a manner to allow substantive review to begin?	X*	
2. Is the pharmacology section of the NDA indexed and paginated in a manner to allow substantive review begin?	X[b]	
3. On its face, is the pharmacology section of the NDA legible so that substantive review can begin?	X	
4. Are all required(*) and requested IND studies completed and submitted in this NDA (carcinogenicity, mutagenicity, teratogenicity*, effects on fertility*, juvenile studies, acute adult studies*, chronic adult studies*, maximum tolerated dosage determination, dermal irritancy, ocular irritancy, photocarcinogenicity, animal pharmacokinetic studies, eta)?	X[c]	
5. If the formulation to be marketed is different from the formulation used in the toxicology studies, has the sponsor made an appropriate effort to either repeat the studies using the marketed product or to explain why such repetition should not be required?	X	
6. Are the proposed labeling sections relative to pharmacology appropriate (including human dose multiples expressed in either mg/m or comparative serum/plasma levels) and in accordance with 201.57?	X[d]	
7. Has the sponsor submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor?	X[e]	

* Red index of studies
b " " " "
c w: flocculation as requested
d no - but can recalculate
e no - no infusion studies as requested

8. On its face, does the route of administration used in the animal studies appear to be the came as the intended human exposure route? If not, has the sponsor submitted rationale to justify the alternative route? X

9. Has the sponsor submitted a statement(s) that all of the pivotal pharm/tox studies been performed in accordance with- the GLP regulations (21 CFR 58) or an explanation for any significant deviations? X

10. Has the sponsor submitted a statement(s) that the pharm/tox studies have been performed using acceptable, state-of-the-art protocols which also reflect agency animal welfare concerns? X

11. From a pharmacology perspective, is this NDA fileable? If "no", please state below why it is not. X f

Reviewing Pharmacology Officer /S/

Team Leader /S/ 2/2/95

f need TOC with index to studies

Filing Meeting (2/3/99)

NDA 21-038
Drug name: [redacted]: (dexmedetomidine HCl) 100 mcg/mL fc [redacted]
Applicant: Abbott Labs, Inc.
Drug class:
Indication: to provide sedation in the adult ICU setting

Volumes received: 1.1, 1.3, 8/10-1 to 242 dated 18 December 1998
(Received HFD-170 21 December 1998)
Reviewer: Z. Jonathan Ma, Ph.D., HFD-720
User fee date:

Project manager: David Morgan
Medical reviewer: Charles Cortinovis, M.D.

1. INTRODUCTION

Clinical studies with [redacted] re conducted under [redacted] his NDA submission contains the study reports and summaries for the following Phase II/III studies conducted by the sponsor:

ICU Sedation Studies – W97-245 (Phase III), W97-246 (Phase III), and W97-249 (Phase II).

Other – Dex-95-002, Dex-95-004, Dex-96-012, Dex-96-014, Dex-96-015, Dex-96-016, Dex-65-021, and Dex-95-023.

For this specific indication, the sponsor identified the three ICU sedation studies above as the pivotal studies.

2. Study Design of the Pivotal Studies

Phase II Study W97-249 was designed to evaluate response in a target clinical population titrated to a protocol-specified level of sedation. Thereafter, two Phase III studies, W97-245 and W97-246, were initiated and followed a common design, differing only in the allowed sedation rescue medication.

Study W97-249 was a one-center study which enrolled a total of 24 patients, 12 in the open-label part and 12 in the double-blind part. The study design was similar to those of studies W97-245 and W97-246, which are summarized in the following.

Summary of Study Design of W97-245 and W97-246		
	W97-245	W97-246
Overall Design	Multicenter, two-part Part I: open label Part II: randomized, double-blind, placebo-controlled	
Study drug	Dex 0.2 to 0.7 mcg/kg/h	
Indication	ICU sedation and analgesia in postop patients	
Study Phase	III	
Primary Endpoints	Total dose (mg) of midazolam/propofol* during intubation received as rescue medication for sedation during study drug administration	
Secondary Endpoints	Total dose (mg/h) of morphine during study drug infusion Total dose (mg) of morphine by time period Total dose (mg) of midazolam/propofol* during study drug administration Etc.	
Rescue Medication	Midazolam for sedation (0.02-mg/kg IV boluses) and morpine for pain (2-mg IV boluses)	Propofol for sedation (0.2-mg/kg IV boluses) and morpine for pain (2-mg IV boluses)
Study Site	33 centers in 10 countries	36 centers in 11 countries
Sample Sizes	Part I: 85	Part I: 92
	Part II: 178 Active and 175 Placebo	Part II: 203 Active and 198 Placebo

*Midazolam for Study W97-245 and propofol for Study W97-246.

Statistical Methods

Only patients from Part II of the two studies were included in the efficacy analyses. Intent-to-treat analyses and evaluable subsets analyses were performed. Descriptive statistics and ANOVA models were used to analyze the efficacy endpoints.

Filing Issues

1. Volume numbering is confusing, two sets of numbering systems

2. Indices are confusing and inadequate, e.g.:

- lists of tables and figures do not have either volume # or page #
- there are two numbering systems for source tables
- indices for appendices do not have either volume # or page #
- could not locate the original protocols of the pivotal studies.

3. Did not find efficacy analyses by age, gender and race.

4. No electronic data was submitted.

Filing Meeting February 3, 1999 (10:00 a.m. 11:30 a.m.)

NDA: 21-038

Sponsor: Abbott Laboratories
Drug: [redacted] (dexmedetomidine HCl) [redacted]

Indication: Provides for sedation in the adult ICU setting.

FILEABILITY:

On initial overview of the NDA application: (YES) NO

BIOPHARMACEUTICAL:

1. On its face, is the biopharmaceutics section of the NDA organized in a manner to allow substantive review to begin? yes
2. Is the biopharmaceutical section of the NDA indexed and paginated in a manner to allow substantive review to begin? yes
3. On its face, is the biopharmaceutics section of the NDA legible so that substantive review can begin? yes
4. Are the Phase studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product? yes
5. If several formulations of the product were used in the clinical development of the product, has the sponsor submitted biopharmacoutics data to allow comparison between the product to be marketed and the product(s) used in the clinical development? N/A
6. From a biopharmaceutic perspective, is the NDA fileable? If "no", please state below why it is not? yes

Reviewing Biopharmaceutics Officer /S/ 2/1/99

Team Leader /S/ 2/1/99